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Five-year longitudinal evaluation of mild primary hyperparathyroidism — medical treatment *versus* clinical observation

Pierwotna nadczynność przytarczyc o niewielkim nasileniu — porównanie leczenia farmakologicznego i obserwacji klinicznej w ramach trwającego pięć lat badania klinicznego

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Abstract

Introduction: Primary hyperparathyroidism (PHPT) is an increasingly common endocrine disorder. Most patients with PHPT do not have disease-specific symptoms. The management of these patients has been widely debated. Recent studies have shown the importance of following up asymptomatic patients in order to reduce co-morbidity. However, there are conflicting opinions as to medical management.

The aim of our study was to compare the outcome of PHPT patients on antiresorptive therapy *vs.* observation only.

Material and methods: We longitudinally evaluated 157 PHPT patients (126 females) aged 22–90 years. Patients who did not undergo surgery were divided into two groups: those on anti-resorptive therapy (N = 52), and those without any treatment (N = 37). Patients who were disease-free after surgery (N = 50) served as controls.

Results: The values of serum calcium (S-Ca), parathyroid hormone (PTH) and indices of bone metabolism did not differ significantly among the three groups of subjects. No differences in 25(OH)-vitamin D levels were noted. Bone mineral density (BMD) was not significantly different at the spinal level. Finally, we found no evidence of an effect of medical treatment on quality of life (QoL). However, QoL significantly improved in the surgery group after parathyroidectomy (PTX).

Conclusions: This study provided up-to-date information in terms of biochemical progression on the natural history of PHPT patients. No significant differences emerged between anti-resorptive therapy and observation only. It is not yet possible to assess the effect of pharmacological treatments on QoL in statistical terms. **(Endokrynol Pol 2014; 65 (6): 456–463)**

Key words: *primary hyperparathyroidism; PHPT; medical treatment; clinical observation; longitudinal evaluation; parathyroidectomy*

Streszczenie

Wstęp: Pierwotna nadczynność przytarczyc (PHPT) jest coraz częściej spotykanym zaburzeniem endokrynologicznym. Większość dotkniętych nim pacjentów nie ma szczególnych objawów podmiotowych, a metody leczenia schorzenia pozostają przedmiotem dyskusji. Najnowsze publikacje wskazują na konieczność obserwowania pacjentów bezobjawowych, co ma na celu zmniejszenie zapadalności na schorzenia współistniejące. Opinie na temat leczenia farmakologicznego są jednak podzielone. Celem niniejszego badania było porównanie przebiegu PHPT u pacjentów przyjmujących leki zmniejszające resorpcję kości i u pacjentów poddanych jedynie obserwacji.

Materiał i metody: Przeanalizowano dane 157 pacjentów (w tym 126 kobiet) w wieku 22–90 lat chorujących na PHPT. Pacjentów nieleczonych chirurgicznie podzielono na dwie grupy: grupa leczonych preparatami hamującymi resorpcję kości (n = 52) i grupa nieleczona farmakologicznie (n = 37). W grupie kontrolnej znaleźli się pacjenci bez objawów choroby po zabiegu chirurgicznym (n = 50).

Wyniki: Stężenia wapnia w surowicy (S-Ca), aktywność parathormonu (PTH) i wskaźniki metabolizmu kostnego nie różniły się istotnie w trzech badanych grupach pacjentów. Nie stwierdzono różnic pod względem stężenia witaminy 25-OH-D (hydroksycholekalcyferolu). Gęstość mineralna kości (BMD) w obrębie kręgosłupa nie różniła się istotnie pomiędzy grupami. Nie stwierdzono też wpływu farmakoterapii na jakość życia (QoL). Odnotowano jednak, że QoL poprawiła się istotnie po zabiegu paratyreoidektomii (PTX) w grupie operowanej.

Wnioski: Niniejsze badanie przynosi informacje na temat naturalnego przebiegu i zmian biochemicznych u chorych na PHPT. Nie stwierdzono istotnych różnic pomiędzy grupą pacjentów leczonych preparatami hamującymi resorpcję kości a pacjentami nieleczonymi. Nie można jednak było ocenić statystycznie wpływu leczenia farmakologicznego na QoL. **(Endokrynol Pol 2014; 65 (6): 456–463)**

Słowa kluczowe: *pierwotna nadczynność przytarczyc; PHPT; leczenie farmakologiczne; obserwacja kliniczna; badanie w układzie podłużnym; usunięcie przytarczyc*

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Introduction

Primary hyperparathyroidism (PHPT) is a disorder characterised by inappropriately high secretion of parathyroid hormone (PTH). PHPT has become a common disease, with an estimated prevalence of 1% of the general population and 3% in postmenopausal women [1], and an increasing incidence over the last few decades.

PHPT is usually the result of a single over-active parathyroid gland as a result of adenoma, hyperplasia or cancer [2]. The clinical presentation has changed over the years: today, 80–85% of cases are asymptomatic [3]. A National Institutes of Health consensus panel has recognised two forms of the disease: asymptomatic and symptomatic [4]. The diagnosis is based on the clinical and objective picture, evaluation of serum calcium (S-Ca) and PTH. Preoperative localisation studies are required.

Therapy may involve medical or surgical treatment, and many guidelines have been proposed over the years. Although parathyroidectomy (PTX) is regarded as the treatment of choice for patients with symptomatic hypercalcaemia or evidence of target organ damage [5], conservative management has been favoured in asymptomatic patients. In addition, in some cases surgery fails, in some it is contraindicated, and in others it is refused [6]. At the most recent International Workshop [7], the guidelines pointed out that there was no data to support the medical treatment of patients with mild PHPT. In general, it is recommended that patients who do not meet surgical criteria [7] be monitored closely. However, the validity of medical treatment is unanimously recognised. The prognosis of PHPT patients depends on the time-line of the diagnosis.

The aims of our five-year study were: 1) to evaluate patients with PHPT during the course of different types of treatment; and 2) to evaluate quality of life (QoL) in PHPT subjects by means of several instruments, both self-rated and physician-administered.

Material and methods

Patients

We longitudinally evaluated all patients (aged 22–90 years) with a history of PHPT in our endocrine unit from 2007–2011. Over the years, the number of patients progressively increased. Patients (N = 18) on cinacalcet were excluded from the study owing to their small number. The remaining study population was divided into three groups: 52 patients were on anti-resorptive therapy (bisphosphonate-treated group: alendronate 70 mg/week N = 22, risedronate 150 mg/month N = 13, ibandronate 150 mg/month N = 11, clodronate 100 mg/week N = 6); 37 were not on any treatment (untreated group); and 50 were disease-free after surgery (surgery group). When required, patients underwent supplementation with vitamin D (< 25mmol/L = 2,000 U/day, 25–50 mmol/L = 1,000 U/day, 50–75 mmol/L = 800 U/day, as reported in the guidelines SIOMMMS).

Written informed consent was obtained from all participants.

Study design

Evaluation was based on clinical examination, neck ultrasonography, bone mineral density (BMD) and blood tests. S-Ca and PTH levels were recorded on each occasion. Serum phosphorus, 25hydroxy-vitaminD (25OHD) and 1.25dihydroxy-vitaminD (1.25OHD), creatinine, total and bone-specific alkaline-phosphatase (ALP), urinary cross-links and osteocalcin were measured annually. Finally, an Italian ad hoc parathyroid questionnaire (PQ) was administered to all patients, to evaluate their QoL. On entry to the study, a semi-structured clinical interview was conducted by a psychiatrist. All subjects were then asked to complete the Italian version of the self-rated Kellner symptom questionnaire (KSQ) [8].

Laboratory evaluations

PTH was analysed by means of two chemiluminescence immunoassays (2007-2008: Immunolite2000, Diagnostic Products, San Juan Capistrano, CA, USA; from 2009: LIASON N-tactPTH, DIASorin, Saluggia, Italy). Reproducibility of the data yielded by the two methods was excellent. The reference range (r.r.) is 15–65 ng/L or < 36.8 ng/L. Creatinine (r.r., 44.0–115.0 μmol/L), S-Ca (2.1–2.7 mmol/L), phosphorus (0.8–1.4 mmol/L), and ALP (98.0–280.0 U/L) levels were determined by means of fully automatic equipment (ModularP800, Roche Diagnostics). Evaluation of 25OHD was performed by means of a chemiluminescence method (LIAISON, DIASorin). A range of 75–250 nmol/L was considered indicative of adequate vitamin D intake. Evaluation of 1.25OHD (r.r. 47.6–150 pmol/L) was performed by radioimmunoassay (Immunodiagnostic Systems). Osteocalcin (r.r. 0.5–7.0 ng/mL) was measured by means of an immunochemiluminescence method (Nichols). Urinary cross-links (expressed as the molar ratio of creatinine) were measured by high-performance liquid chromatography (BioRad, Milan, Italy).

Imaging

Colour-Doppler neck ultrasonography (AU5Idea and MyLabFive; Esaote, Genoa, Italy) was performed by means of a device equipped with a linear 7.5–10 MHz probe. When indicated, fine-needle aspiration was

performed and PTH was evaluated in fine-needle washing in order to locate hyperfunctioning parathyroid tissue [9, 10]. BMD (gr/cm^2) in the lumbar spine and total hip was measured in the antero-posterior direction by means of a dual-energy X-ray absorptiometry technique (DXA) using Hologic instruments (QDR1500 and DQR4500, Bedford, MA). BMD was expressed as a T-score. The so-called standard deviation (SD) scores were calculated from the following equation: T-score = (BMD measured–BMD of a sex- and age-matched population)/SD. DXA was also evaluated at the baseline and each year.

Survey measurements

The ad hoc PQ was prepared as a simplified version of the medical outcome study 36-item short-form survey (SF-36), which is a well-validated measure of general health status [11]. PQ comprised 39 questions, grouped into eight items designed to explore changes in general health perception, physical function, presence/absence of physical pain, social relations, mental health, osteoarticular pain, tiredness or vitality, and specific symptoms. PQ was scored by assigning one point for each negative reply (no physical or mental changes) and two points for each positive reply (physical or mental changes). The total score ranges from 39-78 [12].

The self-rated KSQ had already been used by us [12] and others [13] in similar studies. KSQ comprises eight subscales. The items anxiety, depression, somatisation and hostility evaluate the degree of psychological discomfort or lack of well-being on a numerical scale ranging from 0–23 for each item. The higher the score, the lower the QoL.

Statistical analysis

In accordance with the classification of the WHO, osteoporosis was defined as a T-score < –2.5 and osteopenia as a T-score between –2.5 and –1.0. Data was analysed by means of GraphPad Prism for Windows (Version4.0; GraphPad Software, San Diego, CA, USA). All values are expressed as mean ± standard error of mean (SEM) unless indicated otherwise. To evaluate changes in experimental parameters during the five-year study, the non-parametric Kruskal-Wallis analysis of variance (ANOVA), followed by Dunn's Multiple Comparison test, was used. To compare absolute and percentage data, Mann-Whitney and Chi-square tests were used. Correlation analyses between variables were carried out by means of the Spearman correlation. Data below the functional sensitivity or above the standard curve of the assays were analysed for statistical purposes by using the functional sensitivity value or the maximal value of the standard curve. Significance was taken as P-value ≤ 0.05.

Results

Clinical data

In total, 157 patients with PHPT were followed up. Inter-group comparison by means of ANOVA revealed no significant differences in age (65.2 ± 14.0 years ± SD; P = 0.07), female:male ratio, or smoking (Appendix I). In the study population, mean body mass index (BMI) was 28.8 ± 5.2 kg/m^2. Similar numbers of patients were overweight (BMI = 25–30 kg/m^2) in the three study groups (patients with/without therapy, N = 38, 44%, and surgery group, N = 26, 52%). Eighty-three patients underwent one or more PTX. Histology revealed parathyroid adenoma in most cases (N = 66; 79.5%) or hyperplasia (N = 7; 8.4%), and parathyroid carcinomas in three patients; histopathology data from the remaining (N = 10) patients could not be retrieved. About 50% of no-PTX patients (N = 37) were already symptomatic at the time of diagnosis, while 48% (N = 40) of those who had undergone surgery were symptomatic. At the time of diagnosis, 83 patients were symptomatic for kidney stones (N = 37), bone and joint pains (N = 24), osteoporosis (N = 23), pathological fractures (N = 5), and pancreatitis (N = 2).

Laboratory data

The untreated group and the bisphosphonate-treated group showed similar reductions in S-Ca and PTH concentrations over the five-year follow-up. However, both groups differed significantly from the surgery group: PTH levels (P = 0.05) in the untreated group (P = 0.01) were significantly higher than in the surgery group; S-Ca levels (P = 0.0001) were lower in the surgery group than in the other two groups (Fig. 1).

In all PTX patients, there was a significant difference (P < 0.001) between pre-surgical and post-surgical S-Ca levels. However, while PTH levels remained essentially unchanged in the bisphosphonate-treated group before and after the initiation of drug therapy, serum levels of the hormone were significantly (P < 0.001) reduced after PTX.

Over the five-year study period, a significant reduction in PTH levels was seen only in the surgery group (P < 0.01); in the bisphosphonate-treated group, PTH levels tended to remain stable. A slight, non-significant increase in PTH levels was found in the untreated group. Similarly, S-Ca levels showed a significant reduction only in the surgery group (P < 0.05).

On final evaluation, other biochemical indices did not differ significantly among the three groups. Finally, 48 (28.9%) patients showed Vitamin D deficiency (VDD) (25OHD < 50 nmol/L). These subjects received replacement treatment with cholecalciferol (bisphosphonate-treated group N = 33, mean dose 822.5 ± 158.6 U/day; surgery group N = 27, mean dose 737.5 ± 181.3 U/

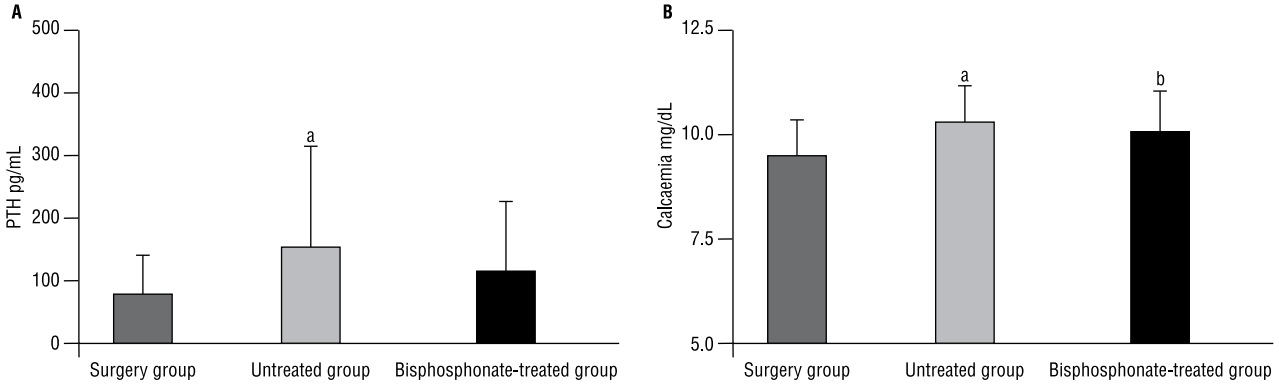

Figure 1. *PTH and S-Ca levels in the surgery group (subjects deemed disease-free after surgery, N = 50), untreated group (patients without medical therapy or surgery, N = 37), and bisphosphonate-treated group (patients on anti-resorptive treatment with bisphosphonates, N = 52). PTH displayed a significant difference (ANOVA P<0.05) between patients deemed disease-free after surgery and those without any therapy* **(A)**; *regarding S-Ca, significant differences (ANOVA P = 0.001) emerged between patients deemed disease-free after surgery and those without therapy (A) and between patients deemed disease-free after surgery and those on bisphosphonate therapy* **(B)**

Rycina 1. *Aktywność PTH i stężenie wapnia w surowicy (S-Ca) w grupie operowanej (pacjenci bez objawów choroby po zabiegu operacyjnym, n = 50), w grupie nieleczonej (pacjenci nieleczeni farmakologicznie ani operacyjnie, n = 37) i w grupie leczonej bisfosfonianami (pacjencji leczeni bisfosfonianami w celu hamowania resoprcji kości, n = 52). Stwierdzono istotną różnicę aktywności PTH (ANOVA p < 0,05) pomiędzy pacjentami bez objawów choroby po zabiegu operacyjnym a pacjentami nieleczonymi w ogóle* **(A)**. *Istotne różnice pod względem S-Ca (ANOVA p = 0,001) stwierdzono pomiędzy pacjentami bezobjawowymi po zabiegu chirurgicznym a pacjentami nieleczonymi (A) oraz pomiędzy pacjentami po zabiegu operacyjnym a pacjentami przyjmującymi bisfosfoniany* **(B)**

Table I. ***Clinical, biochemical and instrumental parameters in all groups of patients on initial evaluation and on last follow-up evaluation (5 years). Data are expressed as mean ± SD unless otherwise specified***

Tabela I. ***Kliniczne, biochemiczne i instrumentalne parametry we wszystkich grupach chorych podczas wstępnej oceny i ostatniej kontroli (5 lat). Dane wyrażono jako średnie ± SD, jeśli nie określono inaczej***

Parameter	Surgery-group		Bisphosphonate-treated group		Untreated-group	
	Initial	Final	Initial	Final	Initial	Final
Number of patients	30	50	22	52	12	37
Female/male	21/9	31/19	19/3	40/12	10/2	31/6
Age (mean years)	61.5 ± 12.3	62.2 ± 1.9	71.7 ± 9.2	68.3 ± 1.6	62.1 ± 17.5	63.2 ± 1.9
BMI [kg/m^2]	27.3 ± 4.3	27.4 ± 5.4	25.9 ± 4.3	26.2 ± 4.8	25.6 ± 5.5	26.2 ± 2.6
Smoking (%)	25	16	8	7	0	5
Time since diagnosis (years)	4.1 ± 5.8	7.0 ± 5.9	2.7 ± 3.0	5.4 ± 4.0	3.2 ± 4.9	5.6 ± 5.3
Creatinine [μmol/L]	79.6 ± 17.7	79 ± 18	61.9 ± 17.7	88 ± 35	70.7 ± 17.7	79 ± 9
S-Ca [mmol/L]	2.4 ± 0.7	2.4 ± 0.0	2.5 ± 0.2	2.5 ± 0.2	2.4 ± 0.2	2.6 ± 0.2
PTH [ng/L]	158.9 ± 29.1	76.1 ± 9.3	204.6±56.9	112.7 ± 111.7	109.9 ± 74.4	152.5 ± 26.3
Total ALP [U/L]	180.8 ± 61.5	144.0 ± 42.0	206.6 ± 56.4	158.3 ± 58.5	173.2 ± 54.0	185.2 ± 73.4
25OHD [nmol/L]	43.7 ± 24.2	64.2 ± 27.2	39.0 ± 20.2	50.2 ± 22.7	48 ± 24.7	40.7 ± 25.2
1.25OHD [pmol/L]	224.0 ± 115.9	255.2 ± 110.9	291.4 ± 151.5	278.3 ± 144.8	299.5 ± 102.4	311.0 ± 130.3
Lumbar spine (T-score)	–1.99 ± 0.9	–1.75 ± 1.2	–2.08 ± 1.4	–2.18 ± 1.7	–1.80 ± 1.6	–1.54 ± 1.2
Total femur (T-score)	–1.33 ± 0.8	–1.50 ± 0.3	–1.88 ± 0.9	–0.19 ± 1.8	–1.98 ± 1.2	–2.96 ± 0.9
Ultrasound TX	30% (N = 9)	36% (N = 18)	9.1% (N = 2)	13.5% (N = 7)	8.3% (N = 1)	8.1% (N = 3)
UNG/MNG	30% (N = 9)	42% (N = 21)	63.6% (N = 14)	53.8% (N = 28)	41.7% (N = 5)	46% (N = 17)
Normal ultrasound pattern	40% (N = 12)	22% (N = 11)	13.6% (N = 3)	21.2% (N = 11)	41.7% (N = 5)	29.7% (N = 11)
Parathyroid pathological	–	–	13.6% (N = 3)	11.5% (N = 6)	8.3% (N = 1)	16.2% (N = 6)

SD — standard deviation; BMI — body mass index; S-Ca — serum calcium; PTH — parathyroid hormone; ALP — alkaline phosphatase; 25OHD — 25-hydroxy-vitamin D; 1,25OHD — 1.25dihydroxy-vitamin D; Tx — thyroidectomy; UNG — uninodular goitre; MNG — multinodular goitre; NS — not significant

day; untreated group N = 16, mean dose 896.1 ± 296.1 U/day). Only the surgery group showed significantly lower 1.25OHD levels than the untreated group (P = 0.001). All data from the first and last observation periods is set out in the Appendix I.

Instrumental data

Each year, ultrasonography was used to search for any sites of parathyroid tissue (Table I).

BMD at the spinal level was not significantly different among the three groups of subjects (P = 0.1). T-scores were mildly, but not significantly, increased in the lumbar spine and unchanged at the femur level five years after observation or therapy.

Quality of life

No significant differences in QoL scores emerged among the three groups of subjects (score: bisphosphonate-treated group 60.3 ± 8.9; untreated group 53.7 ± 17.9; surgery group 48.0 ± 6.7; ANOVA, P = 0.06). In the surgery group, however, QoL improved significantly after PTX (Wilcoxon, P = 0.05) (Fig. 2). Among PTX patients, 76% were satisfied with their PTX.

In semi-structured interviews of 28 subjects (21 females/ /seven males, age 63.4 ± 15.7 years), the psychiatric evaluation performed did not detect any improvement in psychopathology. In the majority of cases in which psychopathology was present, this was minor (anxiety, anxiety-depression, reactive depression); it was major in four (3%) patients (N = 1 potomania or psychogenic polydipsia; N = 1 panic attacks, N = 2 major depression). Concomitant psychopathological events proved to be more frequent in women (males N = 2, females N = 14). The overall scores of the items on the self-rated KSQ were: anxiety 7.7 ± 3.5, depression 7.2 ± 5.3, somatisation 9.9 ± 6.1, and hostility 4.9 ± 4.8. The correlations between age and KSQ scores, and between PTH and KSQ scores, were not statistically significant, nor was the correlation between KSQ and the duration (in months) of disease. No significant difference in KSQ scores emerged between females and males.

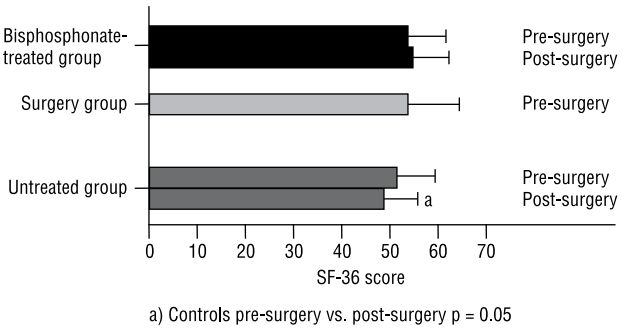

Figure 2. *Evaluation of pre- and post-surgery QoL by means of SF-36 scores in the three groups of subjects studied. A statistically significant difference was seen only in the surgery group (patients deemed disease-free after surgery)*

Rycina 2. *Badanie jakości życia (QoL) przy użyciu kwestionariusza SF-36 przed i po zabiegu operacyjnym w trzech grupach pacjentów. Statystycznie znamienną różnicę odnotowano tylko w grupie operowanej (pacjenci bez objawów choroby po zabiegu chirurgicznym)*

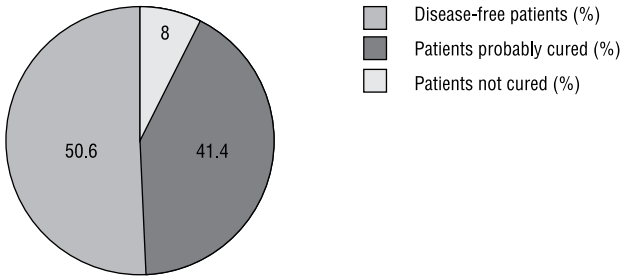

Figure 3. *Distribution of prognoses in PHPT patients who underwent surgery. Both S-Ca and PTH concentrations normalised postoperatively in only 50.6%. In patients who underwent surgery, the clinical course and S-Ca levels prompted us to define the 8% of patients with hypercalcemia as 'not cured'. In many patients (41.4%), S-Ca reverted to the normal range, while serum PTH concentration remained elevated*

Rycina 3. *Rokowanie u pacjentów chorych na PHPT po leczeniu chirurgicznym. Stężenie S-Ca i aktywność PTH uległy normalizacji po usunięciu przytarczyc tylko u 50,6% operowanych. Przebieg kliniczny i wartości stężeń S-Ca w tej grupie skłoniły autorów do stwierdzenia, że 8% pacjentów mających nadmierne stężenie wapnia w surowicy nie zostało wyleczonych ("not cured"). U wielu operowanych osób (41,4%), wartości S-Ca uległy normalizacji, natomiast aktywność PTH w surowicy pozostała zwiększona*

Discussion

Epidemiological considerations

The mean age of PTX patients was lower than that of the other groups. This is compatible with the fact that older people tend to have more co-morbidities (contraindications for surgery) and with the guidelines [7], which state that operable patients should be < 50 years old.

In our study, as in numerous epidemiological studies [10], PHPT was seen to be more frequent in females (N = 126, 77%) than in males (23%). Adenomas accounted for the majority of cases. These findings reflect the normal histological distribution of PHPT, which is supported by a solitary adenoma in 85–90% of cases [14].

BMI was higher in PTX patients. The reason for this is unclear. Finally, although smoking is a risk factor for osteoporosis, there was no significant difference between the number of smokers/past-smokers and non-smokers in our study.

Considerations on treatments

In the PTX patients, in agreement with previous evidence [15], we recorded a high surgical success rate. However, in many patients, PTH concentration remained elevated (Fig. 3); these findings are in line with those of the literature, although this is usually only seen in 20% of patients or less. It is also possible that some of these patients may have been suffering from VDD: vitamin D supplementation after PTX can reduce the incidence of increased PTH. In our series, the untreated patients had higher than average S-Ca values over time, while in the majority of our patients PTH remained stable or decreased over the five-year follow-up. As previously demonstrated [6], bisphosphonates do not normalise the levels of S-Ca and PTH. Likewise, in our series, all indices of bone metabolism differed only slightly in the bisphosphonate-treated group**.** Bisphosphonates are known to be effective in reducing bone turnover in PHPT patients [16]. However, we did not detect a significant difference in BMD in the subgroup treated. More recent data suggests that patients who have normal S-Ca levels after PTX, but elevated PTH, show no improvement in BMD comparatively [17]. This could explain why patients in all three groups displayed the same BMD changes.

Thus, medical management is a helpful alternative to PTX in patients for whom surgery is contraindicated or refused and in those patients with PHPT that relapses after surgery. Medical treatment is based on the use of bisphosphonates, oestrogens, modulators of oestrogen receptors and calciomimetics [18]. Antiresorptive therapy may be an effective therapeutic approach in those patients with low BMD, in order to prevent further bone loss and to reduce the risk of fracture [19]. Moreover, a recent meta-analysis concluded that the effects of PTX and bisphosphonates were similar in mild PHPT [20]. Furthermore, PHPT patients have slightly lower 25OHD levels than controls, despite supplementation. Indeed, PTH induces renal conversion of 25OHD to 1.25OHD; integration may therefore require higher doses than in healthy subjects.

However, we recommend vitamin D substitution before a final decision on treatment is made. Evidence that treatment with vitamin D reduces PTH levels and bone turnover in mild PHPT has been provided by case studies and uncontrolled/controlled cohort studies.

Quality of life

The clinical presentation of mild PHPT may include non-specific symptoms [21] that may affect QoL. In recent years, interest in QoL has grown in some endocrinological fields. Randomised studies have indicated beneficial effects of surgery on QoL, as surveyed by the SF-36; however, these effects have been minor and inconsistent, and the potential placebo effect of the surgery can never be ruled out [22]. One obstacle to evaluating illness perception in patients with PHPT is the current lack of developed questionnaires.

With regard to the outcome of PHPT patients, it has not been specified that ad hoc SF-36 and Hamilton tests should be administrated before and after PTX. Our ad hoc PQ had been prepared to measure general health status and specific symptoms of PHPT.

Our data shows that persistence of the disease was variable in the different groups. However, we noted that QoL only improved in the surgery group. Indeed, over five years, we documented an improvement in somatic and psychological symptoms related to the presence of disease.

Limitations

Several limitations of our study have to be carefully considered, the first being the number of patients, which was somewhat lower than in other studies in the literature. However, over the years, the number of patients progressively increased and follow-up has now reached five years.

A second major limitation is related to the difficulty of randomising patients, as several types of treatment overlapped in the same subjects.

From a technological point of view, BMD was compared at the spine. Although the wrist is the first site of osteoporosis in PHPT, wrist assessment was rarely performed in most patients.

Conclusions

This study provided up-to-date information in terms of biochemical progression on the natural history of PHPT patients. No significant differences emerged between anti-resorptive therapy and observation only. It is not yet possible to assess the effect of pharmacological treatments on QoL in statistical terms, although QoL appeared to worsen in our bisphosphonate-treated patients. However, the number of medically treated PHPT patients is increasing as a result of the review of surgical indications, the increased incidence of diagnoses in asymptomatic patients, and the development of new drug therapies.

References

1. Yu N, Leese GP, Smith D et al. The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study. Quart J Med 2011; 104: 513–521.
2. Fraser WD. Hyperparathyroidism. Lancet 2009; 374: 145–158.
3. Rubin MR, Bilezikian JP, McMahon DJ et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab 2008; 93: 3462–3470.
4. Bilezikian JP, Potts JTJr, Fuleihan Gel-H et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 2002; 87: 5353–5361.

5. Macfarlane DP, Yu N, Donnan PT et al. Should 'Mild Primary Hyperparathyroidism' be reclassified as 'insidious': is it time to reconsider? Clinical Endocrinol 2011; 75: 730–737.
6. Faggiano A, Di Somma C, Ramundo V et al. Cinacalcet hydrochloride in combination with alendronate normalizes hypercalcemia and improves bone mineral density in patients with primary hyperparathyroidism. Endocr 2011; 39: 283–287.
7. Bilezikian JP, Khan AA, Potts JTJr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab 2009; 94: 335–339.
8. Fava GA, Kellner R. Versione Italiana del Symptoms Questionnaire di Kellner. In: Canestrari R (ed.). Nuovi metodi in Psicometria. Firenze 1982: 51–64.
9. Giusti M, Dolcino M, Vera L et al. Institutional experience of PTH evaluation on fine-needle washing after aspiration biopsy to locate hyperfunctioning parathyroid tissue. J Zhejiang Univ Sci B 2009; 10: 323–330.
10. Abdelghani R, Noureldine S, Abbas A et al. The diagnostic value of parathyroid hormone washout after fine-needle aspiration of suspicious cervical lesions in patients with hyperparathyroidism. Laryngoscope 2013; 123: 1310–1313.
11. Ware JE, Sherbourne CD. The MOS 36-item short-form healthy survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30: 473–483.
12. Giusti M, Melle G, Fenocchio M et al. Five-year longitudinal evaluation of quality of life in a cohort of patients with differentiated thyroid carcinoma. J Zhejiang Univ Sci B 2011; 12: 163–173.
13. Lee J, Yun MJ, Nam KH et al. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid 2010; 20: 173–179.
14. Ruda JM, Hollenbeak CS, Stack BC. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otoryngol Head Neck Surg 2005; 132: 359.
15. Udelsman R, Pasieka JL, Sturgeon C et al. Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009; 94: 366–372.
16. Khan A, Grey A, Shoback D. Medical management of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009; 94: 373–381.
17. Ambrogini E, Cetani F, Cianferotti L et al. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective randomized clinical trial. J Clin Endocrinol Metab 2007; 92: 3114–3121.
18. Marcocci C, Cetani F. Clinical practice. Primary hyperparathyroidism. N Engl J Med 2011; 365: 2389–2397.
19. Bollerslev J, Marcocci C, Sosa M et al. Current evidence for recommendation of surgery, medical treatment and vitamin D repletion in mild primary hyperparathyroidism. Eur J Endocrinol 2011; 165: 851–864.
20. Sankaran S, Gamble G, Bolland M et al. Skeletal effects of interventions in mild primary hyperparathyroidism: a metaanalysis. J Clin Endocrinol Metab 2010; 95: 1653–1662.
21. Silverberg SJ, Lewiecki EM, Mosekilde L et al. Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009; 94: 351–365.
22. Perrier ND, Balachandran D, Wefel JS et al. Prospective, randomized, controlled trial of parathyroidectomy versus observation in patients with ''asymptomatic'' primary hyperparathyroidism. Surgery 2009; 146: 1116–1122.

Appendix I

Załącznik I

First name and Surname ...

Date...

Questionnaire for patients with hyperparathyroidism

For the evaluation of the parameters:

1. General health perception
2. Physical function
3. Presence or absence of physical pain
4. Social relations
5. Mental health
6. Osteoarticular pain
7. Tiredness or vitality
8. Specific symptoms

Answer each of the following questions by marking your choice with a cross.		
1. General health perception		
— Height loss	Yes	No
— Sight impairment	Yes	No
— Malaise	Yes	No
2. Physical function		
— Difficulty moving	Yes	No
— Apathy	Yes	No
— Tiredness	Yes	No
3. Various disorders		
— High blood pressure	Yes	No
— Heartburn	Yes	No
— Abdominal pain	Yes	No
— Excessive thirst/urination	Yes	No
— Weight loss	Yes	No

— Appetite loss	Yes	No
— Diarrhea	Yes	No
4. Social relations		
— Unchanged by the disease	Yes	No
— Improved	Yes	No
— Worsened	Yes	No
— Have your physical health or emotional problems interfered with your social activities with family or friends?	Yes	No
5. Mental health		
— Depression	Yes	No
— Insomnia	Yes	No
— Poor concentration	Yes	No
— Fatigue	Yes	No
— Memory loss	Yes	No
— Anxiety	Yes	No
— Irritability	Yes	No
6. Osteoarticular pain		
— Joint pain	Yes	No
— Bone pain	Yes	No
— Muscle pain	Yes	No
7. Tiredness or vitality		
— Not lively	Yes	No
— Agitated	Yes	No
— Down in the dumps	Yes	No
— No energy	Yes	No
— Despondent	Yes	No
— Exhausted	Yes	No
— Unhappy	Yes	No
8. Specific symptoms		
— Kidney stone	Yes	No
— Vomiting	Yes	No
— Constipation	Yes	No
— Tiredness	Yes	No
— Itching	Yes	No
— Sleepiness	Yes	No